UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: November 15, 2016

SUBJECT: **Chlorpyrifos-Methyl (CPM):** Summary of the combined Hazard and Science Policy Council (HASPOC) and Toxicology Science Advisory Council (ToxSAC) meetings of September 2 and 3, 2015: Recommendation on the need for a comparative cholinesterase assay, subchronic inhalation toxicity study, delayed neurotoxicity (acute in hen), and immunotoxicity study.

PC Code: 059102
Decision No.: N/A
Petition No.: N/A
Risk Assessment Type: Single Chemical Aggregate
TXR No.: 0057247
MRID No.: N/A

DP Barcode: N/A
Registration No.: N/A
Regulatory Action: N/A
Case No.: N/A

CAS No.: 5598-13-0
40 CFR: N/A

FROM: Uma Habiba, Executive Secretary
HASPOC
Health Effects Division (HED) (7509P)

THROUGH: Jeff Dawson, Co-Chair
Anwar Dunbar, Ph.D., Co-Chair
HASPOC
Health Effects Division (HED) (7509P)

TO: Michael Metzger, Branch Chief
Risk Assessment Branch V/VII (RABV/VII)
Health Effects Division (HED) (7509P)

MEETING ATTENDEES:
HASPOC Members: Anna Lowit, Elizabeth Mendez, Jonathan Chen, Michael Metzger, P.V. Shah, Ray Kent, Matthew Lloyd, Jeff Dawson, Jaime D'Agostino, Uma Habiba, Jonathan Leshin, Ronnie J. Bever Jr.

Presenter: Ronnie J. Bever Jr.

Other Attendees: Chris Schlosser, Danette Drew, William Irwin, Karlyn Middleton, Monique Perron, Nancy McCarroll, Yung Yang, Ayaad Assaad, Linda Taylor, Myron Ottley, Austin Wray, Abdallah Khasawinah, Jessica Kidwell, Hannah Pope-Varsalona, Sarah Gallagher, Whang Phang, Anwar Dunbar, Vincent Chen

I. PURPOSE OF MEETING

Risk Assessment Branch (RAB) V/VII is conducting a registration review draft risk assessment for the organophosphate (OP) insecticide chlorpyrifos-methyl (CPM), which is used to control pests on stored grains and in grain storage containers. At the request of RAB V/VII, HASPOC is evaluating the need for a comparative cholinesterase assay (CCA; acute, gestational, and repeated dose for parent and oxon), subchronic inhalation toxicity study, and immunotoxicity study to support CPM registration review. ToxSAC members also participated in the meeting in order to inform the discussion related to how the potential use of chlorpyrifos-ethyl (CPE) data (a more potent structural analog with a complete database) - to bridge across chemicals, may impact the need for CPM studies and endpoint selection.

The CCA (non-guideline study), subchronic inhalation toxicity (870.3465), and immunotoxicity (870.7800) studies were requested in the 2010 CPM scoping document (Drew, 2010, D370119). The registrant, DOW AgroSciences LLC, subsequently requested that the CCA, subchronic inhalation, and immunotoxicity studies conducted with the more toxic analog (CPE) be used to meet the outstanding data requirements for CPM. HED, at that time, agreed that the three CPE studies (CCA, subchronic inhalation, and immunotoxicity) could be "bridged' (i.e., used as surrogates in order to fulfill data gaps) for those types of studies for CPM. HED responded by cautioning that the 'bridged' CPE studies could possibly be used for endpoint selection in CPM risk assessment (Doherty, 2012, D400210). HASPOC reconsidered this decision, using a weight-of-evidence (WOE) approach to include additional chemical-specific information, such as physical-chemical properties, use pattern and potential exposure scenarios, and uncertainties regarding susceptibility for vulnerable life stages for CPM.

II. SUMMARY OF USE PROFILE AND PREVIOUS RISK ASSESSMENTS

CPM (*O,O*-dimethyl-*O*-(3,5,6-trichloro-2-pyridyl)phosphorothioate) is a member of the OP class of pesticides and is registered as an emulsifiable concentrate (EC) for post-harvest use on stored grains and grain seeds (wheat, barley, oats, rice, and sorghum) and for use in empty grain storage facilities (bins and warehouses). CPM use appears to be declining based on information provided by BEAD. Available data shows CPM use on stored grains declining from greater than 100,000 lbs/year in 2004 to just greater than 4,000 lbs/year in 2011. Additional survey data from USDA/NASS determined 500 lbs was applied to post-harvest wheat in 2009. This represents a substantial reduction since the 1999 survey (which indicated 11,000 lbs applied to wheat) and the 2004 survey (which showed 19,000 lbs). Wheat was the only grain crop with reported usage.

Exposures may occur to CPM residues in food (grain and livestock commodities) but not drinking water as a result of application methods and the processes associated with handling and use of treated grains (e.g., post-harvest and storage facilities). Workers may also be exposed to CPM dermally and/or by inhalation (during mixing, loading, and/or applying activities

associated with stored grains and/or treating bins, warehouses and other storage facilities. Application to grains is made by automated spray systems or in some cases with handheld equipment. Exposure to the oxon form is not expected for occupational workers because CPM products are expected to contain insignificant amounts of the oxon, and no significant post-application exposure is expected. Open mixing and loading is used for applications. Applicators do not enter the enclosed storage facilities but rather apply from the outside. Given this, occupational post-application exposures are not expected. There are no residential uses of CPM. Exposure via spray drift is not anticipated based on the current use pattern.

In the risk assessment for CPM performed as part of the registration review process, no bridging was performed from the CPE database, and risk assessments were based on CPM data. AChE inhibition (ChEI) is the most sensitive endpoint in the CPM toxicology database in multiple species, durations, and life stages and is the endpoint used for selection of toxicological points of departure (PODs). The PODs for CPM are based on red blood cell (RBC) ChEI from oral animal studies. For acute dietary exposures, the NOAEL of 1.0 mg/kg/day is from the rat developmental study. OPs also exhibit a phenomenon known as steady-state ChEI. After repeated dosing at the same level, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. Therefore, steady-state exposure assessments were conducted instead of the traditional repeated-dose scenarios. For steady state dietary, dermal, and inhalation exposures, the NOAEL of 1.0 mg/kg/day is from the co-critical rat chronic, subchronic, and developmental studies. Rat prenatal developmental toxicity and reproduction studies provided no evidence of increased susceptibility of the fetuses or offspring. There is no developmental neurotoxicity study for CPM.

For dietary exposures (acute and steady-state) a total uncertainty factor (UF) of 1000X (10X to account for interspecies extrapolation, 10X for intra-species variation, and 10X for database uncertainty factor (UF_{DB}) to account for the uncertainties regarding the potential neurodevelopmental effects identified in epidemiology studies evaluating chlorpyrifos-ethyl) was applied for infants, children, youths, and women of childbearing age (13-49 years old. The 1000X uncertainty factor was also applied to occupational dermal or inhalation exposures.

The acute and steady state dietary (food) exposure estimates, based on DEEM modeling using PDP monitoring data and 100% crop treated, are below HED's level of concern (<100 % acute (a)PAD or steady state (ss)PAD) for all life stages. The most highly exposed population subgroup was children (1-2 years old) at 55% of the aPAD and 45% of the ssPAD.

For occupational combined dermal and inhalation exposures, no risks of concern were identified (based on a LOC of 1,000) for the automated spray system scenarios where open loading systems are used. However, risk concerns were identified for handheld equipment scenarios (combined MOEs < 460) using label-based PPE (i.e., single layer clothing plus gloves and PF5 respirator). Combined dermal and inhalation risks for handheld equipment remain of concern despite consideration of additional PPE.

III. STUDY WAIVER REQUESTS

a. Inhalation Study

In the past, OPP used a set of criteria when considering the scientific information available to waive (or not waive) an inhalation study including the chemical's: (1) the severe irritation and corrosivity; 2) low volatility; 3) large aerosol particle size; 4) Acute Toxicity Category IV and an extrapolated MOE (e.g., MOEs 10 times higher than the target). In 2009, OPP developed an issue paper on risk assessment approaches for semi-volatile pesticides. As part of that issue paper, an analytical comparison was conducted of oral and inhalation experimental toxicology studies. In general, this analysis showed that the degree to which oral PODs were protective of potential inhalation toxicity varied. In many cases the oral POD was protective but in some cases the inhalation PODs were significantly more sensitive. Currently, OPP uses a weight of the evidence (WOE) approach discussed below which builds upon experience using the previously used criteria listed above, and informed by the 2009 SAP. As approaches for route to route extrapolation evolve and improve in the future, OPP may, if appropriate, bring additional considerations into the WOE analysis.

Inhalation exposure can be to vapors, droplets, and/or particles/dusts. The form of this exposure is determined by a number of factors including physical-chemical properties, use pattern, and exposure scenarios. This interim WOE approach considers:

1. **Physical-chemical properties:** Vapor pressure and Henry's law constant are key considerations with respect to the volatilization after sprays have settled. CPM is not expected to volatilize significantly from dry surfaces based on a vapor pressure of 2.2×10^{-5} mm Hg at 25°C but may volatilize from water based on a Henry's Law constant of 4.4×10^{-6} atm-m^3 mol^{-1} at 25°C.

2. **Use pattern and exposure scenarios:** CPM is not likely to form vapor that would contribute to exposure based on the current use pattern (post-harvest application to grain or empty bins), but the occupational scenarios involving handheld equipment may result in aerosol formation. Any application scenario that leads to inhalation exposure to aerosols needs to be considered in the WOE analysis for an inhalation toxicology study waiver request. Risk concerns were identified for all scenarios (combined MOEs <3,000 based on a LOC of 3,000) with both label-specified PPE with the highest risk resulting from mixing/loading/applying (M/L/A) with mechanically-pressurized hand wand equipment (Combined MOE of 12).

3. **Margins of Exposure (MOEs):** The MOE estimates were calculated using the NOAEL (1.0 mg/kg/day) from a CPM oral toxicity study, which remains unchanged from the risk assessment, and should be considered in the WOE analysis for an inhalation toxicology study waiver. In the past, OPP has used MOEs of approximately 10 times higher than the level of concern as a benchmark for granting waiver requests. The 2009 analysis suggests this approach is appropriate for most pesticides, but not all. Under the interim WOE approach, MOEs from 10-100 times greater than the level of concern will be considered in combination with other factors discussed here.

   The CPM worker exposures reflect the steady-state. Since the inhalation LOC is 1000, the inhalation target of HASPOC is 3,000. The 3000X safety factor is comprised of the

standard 100X for inter-species extrapolation and intra-species variability, as well as a 30x FQPA safety factor (SF) for females of child-bearing age, infants, children, and youths to account for uncertainty in the human dose-response relationship for neurodevelopmental effects, as well as the lack of a comparative cholinesterase study. This maximum MOE is consistent with Risk Assessment Forum Technical Panel's report *A Review of the Reference Dose and Reference Concentration Processes* which recommends "limiting the total UF applied for any particular chemical to no more than 3000 and avoiding the derivation of a reference value that involves application of the full 10-fold UF in four or more areas of extrapolation." This maximum of 3000 applies to the interspecies, intraspecies, LOAEL-to-NOAEL, database, subchronic-to-chronic-duration, and modifying UFs.[1] For CPM, the inhalation MOE for M/L for automated spraying of grain is 61,000. Mixer/ loader/ applicator MOEs for the backpack sprayer scenario are 220,000 (including label-specified PF5 respirator). The mixer/ loader/ applicator scenarios for the manually- and mechanically-pressurized handwands (which reflect use of the included label-specified PF5 respirator) are 520 and 5900, respectively. One scenario, mixer/loader/applicators using manually-pressurized handwands, only reaches an inhalation MOE of 1000 with the addition of a PF10 respirator.

4. **Toxicity:** The acute LD_{50} oral toxicity of CPM was Toxicity Category III. Acute dermal and inhalation LD/LC_{50} toxicity and dermal and eye irritation were Toxicity Category IV. No acceptable study was available for skin sensitization. The structurally-similar analog, CPE, was classified as non-sensitizing.

   Like other organophosphates, cholinesterase inhibition (ChEI) is the primary effect of CPM. In a subchronic dietary study toxicity study in rat, the NOAEL for red blood cell and brain cholinesterase inhibition was 1.0 mg/kg/day, and the LOAEL was 10 mg/kg/day in both sexes. The NOAEL for systemic toxicity was 1.0 mg/kg/day and the LOAEL was 10 mg/kg/day based on histopathology (hypertrophy, vacuolation and necrosis) of the adrenal gland. There are no acceptable subchronic dermal or inhalation studies with CPM.

   Prenatal developmental toxicity in rats and rabbits and the rat reproduction studies with CPM provided no evidence of increased susceptibility of the fetuses or offspring (based on ChEI or systemic effects). There is no developmental neurotoxicity study for CPM, but the developmental neurotoxicity study with the closely related CPE did not provide clear indications of increased quantitative susceptibility in the offspring (although there were concerns for qualitative susceptibility in offspring). No developmental toxicity was seen at CPM levels toxic to the maternal animals, and there were no treatment-related increases in external, visceral, or skeletal malformations or anomalies. Although no evidence of quantitative sensitivity in the young has been identified in guideline studies in the CPM toxicity database, epidemiological studies evaluating neurodevelopmental deficits associated with CPE exposure (also with no evidence of increased quantitative susceptibility in guideline studies) have raised uncertainty regarding the potential impact

[1] U.S. EPA. A Review of the Reference Dose and Reference Concentration Processes. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC, EPA/630/P-02/002F, 2002, pp. 4-41 thru 4-47.

of OP exposure on the developing nervous system. As such, the Agency has retained a 10X FQPA UF to account for this residual uncertainty.

In the rat chronic study, the NOAEL and LOAEL for RBC ChE inhibition were established at 1.0 and 50.0 mg/kg/day, respectively, but there were no indications of clinical signs. At 50 mg/kg/day in the rat, body weight decreases, alterations in the adrenals (increased weight, slight to moderate vacuolation with lipid accumulation in the zona fasciculata) were observed. In a chronic mouse study, the LOAEL for systemic effects is 44.0 mg/kg/day for males and 41.5 mg/kg/day for females based on histopathological lesions in the liver, kidney, and adrenal glands (NOAEL is 4.40 mg/kg/day for males and 3.94 mg/kg/day for females).

There is no immunotoxicity study for CPM; however, there was no sign of immunotoxicity for the structurally-similar CPE in the guideline immunotoxicity study at the highest dose tested.

There is no evidence of carcinogenicity following oral exposure to CPM in chronic studies in rats and mice and no mutagenicity concern.

5. **Evidence of Inhalation Toxicity from Related Chemicals:** Previously, the steady-state inhalation point of departure for CPM (NOAEL = 1.0 mg/kg/day) was selected from CPM oral studies (RBC AChE inhibition in co-critical rat chronic and developmental studies). The use of the CPM oral studies is considered protective of inhalation exposures. While there are no subchronic inhalation studies for CPM, there are inhalation studies for CPE, which is ~10X more potent of a ChE inhibitor than CPM orally. ChEI was not observed in the CPE subchronic inhalation studies (5 days per week at 6 hours/day) at the highest attainable vapor concentration (0.3 mg/m^3), indicating no toxicity for inhalation of vapor state CPE. A subchronic inhalation study was not available for CPE as an aerosol; however, in an acute (6 hour) inhalation study on the aerosol, ChEI (lung only) was observed at a concentration of 3.7 mg/m^3 (LOAEL and lowest dose tested). Applying a default 10X LOAEL to NOAEL extrapolation would result in a NOAEL of 0.37 mg/m^3 (0.12 mg/kg/day).

The HASPOC recommends that the subchronic inhalation study be required based on the MOEs of concern using the current oral POD. Consequently, the potential for bridging from the existing CPE inhalation data, based on its structure similarity, physico-chemical property similarity, and greater potency, was discussed with ToxSAC committee members (who were also at the meeting) (i.e., use CPE data as a surrogate). However, it was decided not to use the bridging approach and to apply all appropriate uncertainty factors (30x UF_{DB}, 10x intraspecies, and 10x interspecies).

The HASPOC concludes, based on a WOE approach, that a subchronic-day inhalation toxicity study is required for CPM at this time based upon; 1) the potential for repeated inhalation exposure; and 2) the use of an oral POD results in MOEs greater than appropriate level of concern for all application methods (i.e., 3000 in this case).

b. Comparative Cholinesterase Assay

A CCA study is required for all OPs. Based on a comparison of the toxicity databases of CPM and CPE, it has been established that CPE is 10X more toxic than CPM in adults orally. However, at this time, it is not possible to determine if the same relative potency would be seen across all lifestages. As a result, the Agency concluded that bridging based on CPE data is inappropriate and, therefore, the CCA study (acute, repeated-dose, and gestational in parent) is required.

An oxon CCA study is also typically required. However, for CPM, the oxon is not expected to occur in/on food or in the environment based on the current use pattern. Consequently, the oxon CCA study for CPM will not be required due to a lack of exposure potential.

c. Immunotoxicity

a. Indicators for Potential Immunotoxicity

Parameter	Findings
Hematology Indicators (WBC changes)	None
Clinical Chemistry Indicators (A/G Ratio)	None
Organ Weight Indicators (Spleen, Thymus)	None
Histopathology Indicators (Spleen, Thymus, Lymph nodes)	None
Toxicity Profile (Target Organs)	AChE, Adrenal, Liver, Kidney

Evidence for Immunotoxicity for SAR Chemicals – Retrospective Analysis: In considering the need for an immunotoxicity toxicity study, the Agency will evaluate other pesticides which share the same mode of action (MOA) and/or are in the same class. These pesticides can provide important information with respect to potential immunotoxic effects. Specifically, if other similar pesticides show immunotoxicity studies to be more sensitive, an immunotoxicity study may be required, depending on the exposure profile. The closest structural analog is CPE, which has an immunotoxicity study. In the CPE immunotoxicity study, no immunotoxicity was observed at the highest dose tested.

The risk assessment team suggested to the HASPOC that the immunotoxicity study not be required.

HAPSOC recommends that an immunotoxicity study not be required at this time based on the lack of immunotoxic effects observed in the database of CPM and the lack of immunotoxicity in

the closely related structural analog, CPE (which includes an immunotoxicity study in its database).

IV. HASPOC RECOMMENDATIONS:

Based on a WOE approach considering of all the available hazard and exposure information for chlorpyifos-methyl, the HASPOC concludes that the immunotoxicity study is not required at this time. However, the subchronic inhalation toxicity study and comparative cholinesterase assay (acute, repeated-dose, and gestational in parent only) are required. The ToxSAC supported this approach because it was decided with their input that bridging to CPE is not appropriate and instead an additional UF_{DB} would be applied.

The delayed neurotoxicity study in hen was also brought up in this meeting. HASPOC ruled that the study would not be required, because the more potent structural analog CPE did not demonstrate delayed neurotoxicity and neurotoxicity in the hen with CPM would not be anticipated.